REMARKS

Claims 4-7, 9-15, 17-18, 20-22 and 26-30 are pending in the present application. By the above amendments, Claims 14-15 have been canceled without prejudice, and Claims 10-11, 17-18, 20-22, 26 and 28 have been amended to more particularly point out and distinctly claim the subject matter which applicants regard as the invention. More particularly, independent Claim 10 has been amended to incorporate the limitations previously found in Claims 14 and 15. Claims 11, 17-18, 20-22, 26 and 28 have been amended to clarify the claims. Applicants submit that the amendments are fully supported by the specification as filed and no new matter is being added. After entry of the amendments, Claims 4-7, 9-13, 17-18, 20-22 and 26-30 will remain pending and under consideration.

The Examiner has rejected Claims 11-15, 17, 18 and 27 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the rejection. Specifically, the Examiner objects to the term "comprising" in Claim 11 as being an improper Markush format, and to the term "nicotine cessation and withdrawal" in Claim 28. Applicants have amended Claim 11 as suggested by the Examiner to replace "comprising" with "consisting of", and to delete "nicotine cessation and withdrawal" from Claim 28 thereby obviating this ground for rejection.

The Examiner has rejected Claims 4-7, 9-15, 17-18, 20-22 and 26-30 under 35 U.S.C. §103(a) as being unpatentable over Yang et al. (US 5,576,022) in view of Davis et al. (CA 1326632). The Examiner also cites Chen et al. (6,183,777), and indicates that Chen is equivalent to Yang. The Examiner states:

> Yang discloses a controlled release formulation that comprises an immediate release core that comprises nonpareil seeds, tacrine and a binding agent, a sealing layer or sustained release layer over the immediate release pellets. . . Tacrine is a known cholinesterase-inhibiting agent that is used to treat symptoms [of] Alzheimer's patients.
>
> Although Yang discloses the formulation of the instant invention, the active agent is tacrine instead of galantamine. Galantamine is also acetyl cholinesterase inhibitor that can be used to treat the symptoms of Alzheimer's. Davis discloses sustained release formulation for the treatment of Alzheimer's disease and the formulation comprises particles of galantamine. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the tacrine formulation of Yang to patients in need thereof to treat the symptoms of Alzheimer's. . . .
>
> Chen et al. (US 6,183,777) is equivalent to Yang. Chen discloses controlled release tacrine dosage form that comprises a core, coated on the core is an active inner layer comprising tacrine, a release-controlling layer comprising one or more release controlling film forming polymer, and an active overcoat that comprises tacrine and a binder. . . . Just as is discussed above, it would be obvious to substitute the galantamine of Davis for the tacrine of Chen and expect to treat Alzheimer's disease in patients in need thereof. (citations omitted)

Applicants respectfully traverse this rejection.

By the above amendments, independent Claim 10 has been amended to incorporate the limitation of Claims 14 and 15, i.e., that the formulation further comprises a topcoat comprising galantamine and a water-soluble polymer and wherein the formulation is capable of releasing in USP buffer pH 6.8 at 37°C in a paddle apparatus operating at 50 rpm, from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours.

Although Yang et al. disclose a controlled release formulation of tacrine comprising nonpareil seeds, tacrine and a binding agent, and a sealing layer or sustained release layer over the immediate release pellets, the sustained release compositions described by Yang et al. consists of the immediate release composition covered by a sustaining layer (*see, e.g.*, specification, column 5, lines 63-65). By contrast, amended Claim 10 now requires that the controlled release formulation of the present invention further comprises an immediate release topcoat of galantamine and water-soluble polymer which provides the specified release rate of galantamine from the formulation which is not taught or suggested by Yang et al. Chen et al. disclose a controlled release tacrine dosage form that comprises a core, an active inner layer comprising tacrine coated on the core, a release-controlling layer comprising one or more release controlling film forming polymers, and an active overcoat that comprises tacrine and a binder. However, all of the dosage forms of Chen et al. release significantly less than 20% of the active agent tacrine at 1 hour when tested on USP No. 1 dissolution tester at 50 rpm, at 37 C in HCL media at pH 6.8. (*see*, Example 6 and Figures 1 to 43 of Chen et al.). By contrast, amended Claim 10 requires that the claimed formulation is capable of releasing in USP buffer pH 6.8 at 37°C in a paddle apparatus operating at 50 rpm, from 20 to 40 % of the total amount of galantamine.HBr in 1 hour. Davis discloses a sustained release formulation for the treatment of Alzheimer's disease which comprises particles of galantamine, however, as noted by the Examiner, Davis does not disclose the requirement that the water soluble film forming polymer and galantamine be layered onto inert spheres.

Applicants submit that the cited references, either individually or in combination, would not motivate one of ordinary skill in the art to make the claimed formulation which requires that the formulation has a topcoat comprising galantamine and a water-soluble polymer and that the formulation is capable of releasing in USP buffer pH 6.8 at 37°C in a paddle apparatus operating at 50 rpm, from 20 to 40 % of the total amount of galantamine.HBr in 1 hour, and more than 80 % of the total amount of galantamine.HBr in 10 hours. Thus, Applicants maintain that the cited references do not render the claimed formulation unpatentable, and Applicants respectfully request that the Examiner withdraw the rejection of Claims 4-7, 9-15, 17-18, 20-22 and 26-30 under 35 U.S.C. §103(a).

Additionally, Applicants submit that the instantly claimed galantamine controlled-release ("CR") formulation possesses unexpected advantages over the known commercially available galantamine immediate-release ("IR") formulation. Specifically, the instantly claimed galantamine CR formulation results in an unexpected reduction in nausea and vomiting as compared to the commercially available galantamine IR formulation, and that, in the aggregate, this reduction is not tied to a reduction in the maximum blood plasma concentration as would be expected, but instead, is tied to the rate of rise of blood plasma concentration. *See*, Applicants' earlier response mailed March 6, 2003 on pages 3-4, and the accompanying declaration of Luc Truyen, M.D., Ph.D. under 37 C.F.R. 1.132 mailed the same date. Furthermore, a post-hoc analysis of a previously reported large, randomized,

double-blind, placebo- and active-controlled clinical trial was undertaken to explore the upper gastrointestinal ("GI") tolerability (i.e., nausea and vomiting) of the instantly claimed galantamine CR formulation as compared to the galantamine IR formulation. In this post-hoc analysis, 65.8% of patients on the instantly claimed galantamine CR formulation and 61.3% of patients on the galantamine IR formulation were titrated to a 24 mg/day dose; 16.9% of the galantamine CR formulation patients and 13.8% of the galantamine IR formulation patients reported nausea, and 6.6% of the galantamine CR formulation patients and 8.6% of the galantamine IR formulation patients reported vomiting. However, the duration of upper GI symptoms was lower with the instantly claimed galantamine CR formulation than the galantamine IR formulation, and for the subset of patients who had nausea during the study, this difference was statistically significantly shorter for the claimed galantamine CR formulation. Moreover, the shorter duration of upper GI symptoms was seen despite less anti-emetic usage in patients randomized to the instantly claimed galantamine CR formulation. The findings of this post-hoc analysis, which concluded that the instantly claimed galantamine CR formulation has improved upper GI tolerability as compared to the galantamine IR formulation, was presented as a poster at the 12th Congress of the International Psychogeriatric Association in Stockholm, Sweden, September 20-24, 2005. A copy is provided for the Examiner's convenience. Applicants maintain that the cited references would not motivate one of ordinary skill in the art to make the claimed galantamine CR formulation possessing the advantages as described, and Applicants therefore respectfully request that the Examiner withdraw the outstanding rejections under 35 U.S.C. §103(a).

In view of the above amendments and remarks, Applicant maintains that the application is in condition for allowance and passage to issue is earnestly requested.

Respectfully submitted,

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Gastrointestinal Tolerability of Once-Daily Galantamine in Subjects with Mild-to-Moderate Alzheimer's Disease

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INTRODUCTION

- Galantamine (GAL) a dual-action acetylcholinesterase inhibitor that allosterically modulates nicotinic acetylcholine receptors[1], has shown broad and sustained benefits in patients with Alzheimer's Disease (AD).[2,3,4]
- As with other agents that enhance the cholinergic system, the most common side effects of GAL are upper gastrointestinal (GI) symptoms, such as nausea and vomiting.
- GAL has been available in a twice-daily formulation (GAL-IR). A new prolonged release capsule with a once-daily formulation has been developed (GAL-ER).
- A large, randomized, double-blind, placebo- and active-controlled trial has shown that GAL-ER is safe and effective for patients with mild to moderate AD.[5]
- This post-hoc analysis was undertaken to explore the upper GI tolerability of GAL-ER compared to GAL-IR.

METHODS

Patients

Key Inclusion Criteria

- Probable Alzheimer's Disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria
- MMSE 10-24
- ADAS-cog ≥18
- Cognitive decline that was gradual and progressive over a period of ≥6 months
- Availability of a responsible caregiver who lived in, or visited at least 5 days/week

Key Exclusion Criteria

- Other neurodegenerative disorders
- Other causes of cognitive impairment
- Clinically significant cardiovascular or cerebrovascular disease, psychiatric disease, hepatic, renal, pulmonary, metabolic or endocrine disturbances, epilepsy or clinically significant urinary flow obstruction
- Use of any other agent for the treatment of dementia
- History of drug or alcohol abuse

Design

- Post hoc analysis of a Phase III, randomized, double-blind, placebo-controlled, multicentre 6-month trial of GAL-ER vs. GAL-IR in mild to moderate AD (Brodaty, 2005)[5]
- After a 4-week placebo run-in period, dosage began at 8 mg/day for 4 weeks and was then titrated up to 16 mg/day for an additional 4 weeks, after which the dose could be increased to 24 mg/day at the investigator's discretion based on tolerability. At week 12, subjects receiving 24 mg/day could have their dose decreased to 16 mg/day based on tolerability

Outcome Measures

- Percent of patients reporting nausea/vomiting (N/V)
- Predictors of N/V
- Duration of N/V expressed as a percentage of treatment days on which N/V was reported
- Severity of N/V
- Use of concomitant anti-emetics

RESULTS

- A total of 971 patients were randomized (1:1:1) with 965 receiving a least one dose of study treatment (319 GAL-ER, 326 GAL-IR, 320 Placebo). The post-hoc analysis included the 645 patients in the GAL-ER and GAL-IR groups.
- 65.8% GAL-ER and 61.3% of GAL-IR patients were titrated to a 24 mg/day dose.
- 16.9% of patients in the GAL-ER and 13.8% of patients in the GAL-IR groups reported nausea. 6.6% of patients in the GAL-ER and 8.6% of patients in the GAL-IR groups reported vomiting.
- Female patients and patients with lower body weights were more likely to report nausea. (Table 1)

Table 1. Demographic and baseline characteristics for patients in the GAL-ER and GAL-IR groups.

		GAL-ER		GAL-IR	
Parameter		All Subjects (n = 319)	Subjects with Nausea or Vomiting (n = 60)	All Subjects (n = 326)	Subjects with Nausea or Vomiting (n = 66)
Age (y)	Mean (SD)	76.65 (7.64)	76.58 (7.13)	76.46 (7.77)	76.84 (8.81)
	Median	77.00	76.50	78.00	78.00
	Range	55-93	56-93	49.00-92.00	53.00-92.00
Sex, n (%)	Female	205 (64.26)	48 (80.00)	208 (63.80)	41 (70.69)
	Male	114 (35.74)	12 (20.00)	118 (36.20)	17 (29.31)
Race, n (%)	Black	9 (2.82)	1 (1.67)	12 (3.68)	2 (3.45)
	White	297 (93.10)	58 (96.67)	293 (89.88)	52 (89.66)
	Hispanic	2 (0.63)	0 (0.00)	6 (1.84)	1 (1.72)
	Asian	9 (2.82)	0 (0.00)	5 (1.53)	0 (0.00)
	Other	2 (0.63)	1 (1.67)	10 (3.07)	3 (5.17)
Body mass index*	Mean (SD)	25.39 (4.17)	24.46 (3.83)	25.78 (5.64)	24.96 (4.74)
	Median	24.78	24.25	25.06	24.67
	Range	12.44-39.37	18.90-34.10	12.74-64.20	16.79-37.11
Weight (kg)	Mean (SD)	68.60 (14.16)	65.73 (13.31)	68.29 (15.86)	66.10 (14.82)
	Median	67.30	63.10	67.30	68.20
	Range	35.80-120.90	46.00-94.10	37.00-136.40	39.00-96.50
Height (cm)*	Mean (SD)	164.06 (10.23)	163.54 (9.65)	162.71 (10.85)	162.26 (11.62)
	Median	162.60	162.00	161.00	160.00
	Range	142.00-191.00	142.00-188.00	121.90-206.80	132.00-198.00

* Body mass index and height data were missing for 2 subjects, 1 in the GAL-ER group (without nausea or vomiting) and 1 in the GAL-IR group (with nausea or vomiting). GAL-ER = extended-release galantamine; GAL-IR = immediate-release galantamine.

- Nausea and vomiting were more common during dose titration phase (Weeks 1-12)
- Weekly analysis of the percentage of patients with nausea and/or vomiting during the 12-week titration phase showed lower rates in the GAL-ER group (GAL-ER min 0.3% week 4, max 6.6% week 10; GAL-IR min 1.9% week 3, max 8.1% week 9).
- Analysis of the AUC of the percentage of patients reporting nausea and/or vomiting per day during dose titration (weeks 1-12) suggested a trend toward a lower by day frequency in GAL-ER patients (173.5) compared with GAL-IR patients (320.9) p= 0.054 (Figure 1)
- Nausea was reported on 3.1% GAL-ER and 5.2% GAL-IR treatment days. Vomiting was reported on 0.6% GAL-ER and 1.6% GAL-IR treatment days.
- For patients reporting nausea, the mean percentage (SD) of nausea days was 18.4% (28.2) in the GAL-ER group compared with 38.0% (48.2) in the GAL-IR group (P=0.0138) (Figure 2)
- For patients reporting vomiting, the mean percentage (SD) of vomiting days was 8.5% (14.2) in the GAL-ER group compared with 19.1% (46.7) in the GAL-IR group (P=0.35)
- Severities of nausea and vomiting were similar in the two groups; nausea episodes were rated, as mild/moderate/severe, respectively, in 52/41/7% of the GAL-PRC group and 56/38/6% in the GAL-IR group.
- The use of anti-emetics was 33.3% of the GAL-ER and 53.4% of the GAL-IR patients who reported nausea or vomiting p=0.0281 (Figure 3)

Figure 1. Percentage of patients reporting nausea and/or vomiting during dose titration

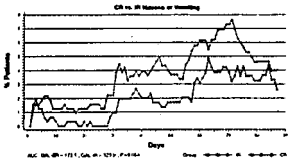


Figure 2. Percent Nausea Days in Patients Reporting Nausea

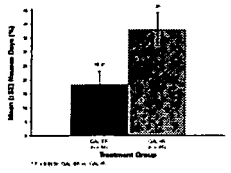
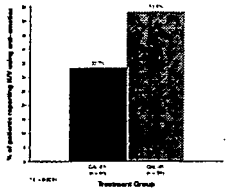


Figure 3. Use of Anti-emetics in Patients Reporting Nausea and/or Vomiting



CONCLUSIONS

- This post hoc analysis showed that the duration of upper GI symptoms was lower with once-daily GAL-ER than twice daily GAL-IR. For patients who had nausea during the study, this difference was statistically significantly shorter for GAL-ER.
- The shorter duration of upper GI symptoms was seen despite less anti-emetic usage in patients randomized to GAL-ER.
- These findings suggest that GAL-ER has improved upper gastrointestinal tolerability compared with GAL-IR.

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